BMJ.2017.041016.R1: "*Outcomes of Non-invasive Diagnostic Modalities for the Detection of Coronary Artery Disease: A Network Meta-analysis of Diagnostic Randomized Controlled Trials*"

December 23, 2017

Editorial Board
British Medical Journal

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Dear Editors,

We were pleased to receive the comments of the editors and the reviewers as well as the opportunity to submit a revised version of our manuscript. We are grateful for the very insightful comments that have helped us to considerably improve our work. We have addressed all of the suggestions/comments in this revised version. In more detail:

****Report from The BMJ's manuscript committee meeting****

Detailed comments from the meeting:

Comment: First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Reply: This has been done below.

Please also respond to these additional comments by the committee:

Comment: * How novel are the recommendations you draw? Is this not already done in many hospital settings? The findings look confirmatory to the 2012 AHA guidelines for the diagnosis and management of patients with stable ischemic heart disease (Circulation. 2012;126:e354).

Reply: Thank you for raising this issue. It is important to bear in mind that all clinical practice guidelines (including the 2012 AHA guidelines on stable coronary artery disease) incorporate not only an evaluation of the evidence, but also a value judgment based on personal or organisational preferences regarding the various risks and benefits of a medical intervention for a population. This was highlighted by a recent evaluation of all US cardiovascular (ACCF/AHA) clinical guidelines, which for cardiovascular imaging, revealed that only 2.4% of recommendations were based on Level A evidence (the highest level). Disappointingly ~17% were based on Level C evidence (the lowest level) and ~44% of cardiovascular imaging recommendations were based on no evidence at all (Tricoci P., et al. JAMA. 2009). This underlines the

importance of conducting further well-designed clinical trials in diagnostic imaging, but also robustly synthesizing the evidence where available.

In this regard, our network meta-analysis is the most comprehensive synthesis of the available evidence derived from relevant diagnostic randomized trials that aim to detect coronary artery disease in patients presented with symptoms suggestive of stable coronary artery disease or low-risk (troponin negative) acute coronary syndromes. To the best of our knowledge, there is no similar work, either published or in progress, in terms of using advanced statistical analyses, for the comprehensive assessment of available comparators, study populations, as well as clinical outcome measures.

In the 2012 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for the diagnosis and management of stable ischemic heart disease, under the section "*2.2.1. Approach to the Selection of Diagnostic Tests to Diagnose SIHD, page e372*" of the guideline document it is reported that "… *No direct comparisons of the effectiveness of a functional approach with inducible ischemia or an anatomic approach assessing coronary stenosis have been completed in the noninvasive setting, although several randomized controlled trials (RCTs) are under way, which will directly or indirectly compare test modalities*…" and under the section "*2.2.1.1. Assessing Diagnostic Test Characteristics, page e372*" of the guideline document it is reported that "… *In practice, although knowledge of the effect of diagnostic testing on outcomes would be highly desirable, the vast majority of available evidence is on diagnostic or prognostic accuracy. Therefore, this information most commonly is used to compare test performance.* …". These sentences well describe the gap of evidence that we attempted to address in the present network meta-analysis. Since the publication of the above mentioned guideline document (2012), several diagnostic randomized controlled trials have been completed and their results have changed the landscape of comparative effectiveness research in imaging of coronary artery disease. More specifically, 10 out of the 12 D-RCTs (information on 20781 out of 22062 of the whole network) of our network meta-analysis for the group of patients with suspected stable coronary artery disease had not been published after the publication of the specific guideline document. Of note, coronary computed tomographic angiography, as the only non-invasive anatomical imaging modality, was not examined in the 2 remaining D-RCTs available before the ACCF/AHA 2012 guideline document. As a result, at the time point of the guidelines document publication there was no available evidence derived from randomized trials on the coronary computed tomographic angiography compared to other noninvasive imaging modalities.

The 2012 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for the diagnosis and management of stable ischemic heart disease adopted a risk stratification approach according to the clinical pretest probability of coronary artery disease as low (<10%), intermediate (10%–90%), or high (>90%). Based on this risk stratification and evidence derived only from studies of diagnostic accuracy and/or non-randomized studies, they made their recommendations in year 2012. However, diagnostic accuracy is not necessarily translated into patient benefits; whereas the inference of effectiveness of diagnostic tests for improving clinical outcomes remains unknown. The most conclusive evidence regarding patient outcomes is derived from diagnostic randomized controlled trials, in which participants are randomized to have a new diagnostic test vs. a control or no test. Performing such trials is challenging, but randomized controlled trials represent a rigorous approach to diagnostic test evaluation and their examination can offer useful

insights. In the case of diagnostic modalities for diagnosis of stable ischemic heart disease, only after the publication of the ACCF/AHA 2012 guidelines document, did the results of many of these diagnostic randomized controlled trials evaluating advanced imaging modalities (namely coronary computed tomographic angiography and cardiac magnetic resonance) became available.

Moreover, the principal investigators of the two largest trials in the field (SCOT-HEART and PROMISE trial) highlight in a recently published review (Fordyce et al., JACC 2016): "*…These 2 large randomized trials and several smaller ones have shown CCTA to be a useful clinical tool (35–38) (Central Illustration). CCTA now appears to have a proven role in management of patients in whom there is uncertainty about the diagnosis of CHD. Clinicians should consider both CCTA and functional imaging when evaluating eligible patients*. ….”; conclusions that are not in line with the guidelines statement of the ACCF/AHA 2012 document. In our comprehensive network meta-analysis, we were able to assess the outcome of “overall downstream testing” (which refers to additional diagnostic investigations required to be performed (invasive and/or non-invasive) after the initial diagnostic test/strategy). This outcome has not been evaluated in any of the previously published conventional (pairwise) meta-analyses (details are provided below as response to Reviewer’s 2 comments). We were able to assess this outcome by means of network meta-analysis, because principal investigators of the eligible diagnostic randomized trials contributed to this analysis by providing unpublished aggregated data. Furthermore, we were able to summarize information on additional patient-oriented outcomes. This has been acknowledged in the main manuscript.

Because of the difficulties in performing diagnostic randomized trials, direct comparisons between contemporary non-invasive imaging modalities is not easy to perform. Our network meta-analysis provides indirect comparative evidence of the advanced imaging modalities that have not been directly tested in diagnostic randomized trials so far (i.e. coronary computed tomographic angiography vs. cardiovascular magnetic resonance). Finally, we mapped in detail the currently available evidence derived from diagnostic randomized trials and their impact on downstream testing and clinical outcomes. Our findings can serve as a platform for planning future clinical trials by defining unanswered questions in the specific field. For the above-mentioned reasons we believe that our meta-analysis is timely, novel and of great interest for the general medical community.

<u>Comment:</u> General readers will appreciate fewer acronyms and better explanation of phrases like "functional testing" and "downstream testing". We suggest a rewrite, with a general reader in mind. All of the acronyms should be spelled out.

<u>Reply:</u> Following this recommendation, we have spelt out all of the acronyms throughout the manuscript. We have also summarized in the following Box 2, a short description of the functional and anatomical tests used for non-invasive assessment of coronary artery disease detection and we have provided further details on the technical terminology used in the manuscript. Specifically the terms of “diagnostic randomised controlled trial”, “functional testing”, “anatomical testing”, “downstream testing”, and “low-risk acute coronary syndrome patients” have been explained keeping the general reader in mind. Box 2 has been included in the main manuscript of the revision.

Box 2: Definitions of terminology used in the study.

Diagnostic randomised controlled trial: Trials in which the randomly assigned comparators refer to diagnostic tests or strategies (typically one is considered to be the control arm and the other(s) the experimental diagnostic strategy) with further clinical management dictated by the individual test/strategy results. Trial end points may include clinical events (outcome measures), patient-reported outcome measures or cost effectiveness.

Anatomical vs functional assessment for the diagnosis and management of coronary artery disease:
Although coronary artery disease is characterised by atherosclerosis of the vessel wall, it only produces symptoms (angina) when the blood flow is restricted to the heart muscle producing myocardial ischaemia. Diagnostic tests for coronary artery disease are thus broadly divided into two groups:
a) Anatomical tests: Invasive (coronary angiography) and non-invasive diagnostic tests (e.g. coronary computed tomographic angiography) that provide structural information specifically on the extent of coronary artery disease (plaque severity) within the coronary artery tree.
b) Functional tests: Diagnostic tests that detect myocardial 'ischemia', typically using either exercise or pharmacological stress to increase cardiac output or coronary blood flow (e.g. radionuclide perfusion imaging, stress echocardiography or cardiovascular magnetic resonance imaging).

Downstream testing: The requirement for additional diagnostic investigations that are performed (invasive and/or non-invasive) after the initial diagnostic test/strategy. Typically this might occur following test failure or diagnostic uncertainty in relation to the index test result.

Low-risk acute coronary syndrome patients: Patients typically presenting with chest pain (or anginal equivalent) of at least 5 minutes duration at rest within the last 24 hours, without history of known coronary artery disease, without diagnostic ischemic changes on the electrocardiogram, without hemodynamic or clinical instability, and an initial troponin level lower than the 99th percentile of the used assay. This group of patients typically does not require immediate assessment by invasive coronary angiography.

Comment: * Please provide, early on in the introduction, a list/description of functional and anatomical tests used for the non-invasive diagnosis of CAD. Also, please provide a box describing the key features of each.

Reply: We are grateful for this comment. We have now amended our Introduction to include the following statement: "… *Nowadays, functional and anatomical non-invasive tests are widely available and used according to locally available resources and expertise: exercise electrocardiogram, single-photon emission computed tomography – myocardial perfusion imaging, stress echocardiography, real-time myocardial contrast echocardiography, coronary computed tomographic angiography and cardiovascular magnetic resonance.* …". The following Box 1 has also been included in the revised

manuscript, summarizing the key features of the above listed diagnostic tests for detection of coronary artery disease.

Box 1: Key features of widely used functional and anatomical tests for the non-invasive diagnosis of coronary artery disease.

Exercise electrocardiogram: This test aims to detect myocardial ischemia indirectly through electrocardiographic changes during exercise and recovery, which is the physiologic consequence of a mismatch between myocardial oxygen supply (coronary blood flow) and myocardial oxygen demand (myocardial work). It is a well validated tool for the assessment of functional capacity and chronotropic response to exercise.

Stress echocardiography: Cardiac ultrasound (echocardiography) is used to evaluate myocardial function (contractility) at rest, and during exercise/pharmacologic stress. It can detect the presence and extent of coronary artery disease by provoking regional ischemia with resulting wall motion abnormalities. Myocardial ischaemia is provoked either by exercise (treadmill or bicycle) or pharmacologic agents (predominantly dobutamine).

Real-time myocardial contrast echocardiography: The test relates to the use of an intravenous echocardiographic contrast agent during stress echocardiography. Whilst echo-contrast agents can be used to improve endocardial border definition in patients with suboptimal echocardiographic images, they also offer visualisation of myocardial tissue perfusion.

Single-photon emission computed tomography – myocardial perfusion imaging: This technique uses intravenous administration of a radioactive myocardial perfusion tracer (radioisotope), to evaluate cardiac perfusion and function at rest and during dynamic exercise or pharmacologic stress. The technique provides information on the presence or absence of myocardial ischaemia, myocardial infarction (and viability), and ventricular function.

Coronary computed tomographic angiography: This test provides direct visualization of the coronary artery lumen and wall using an intravenous contrast agent to produce a computed tomographic coronary angiogram. Preceding non-contrast scans can assess the presence and extent of coronary artery calcium in the vessel wall, which is a marker of extent of coronary atherosclerosis and future risk, but not necessarily related to the severity of coronary artery narrowing.

Stress cardiovascular magnetic resonance imaging: This is an advanced cross-sectional imaging modality which acquires 2D or 3D images of the heart. Using a contrast agent during pharmacologic stress, first-pass perfusion images can be used to identify areas of low myocardial blood flow ('ischemia') or stress-induced regional wall motion abnormalities. During a single study, information is also provided on regional/global resting ventricular function, myocardial infarction (and viability) and proximal coronary artery anatomy.

Comment: *** Although this is a review of diagnostic testing it is not answering a question of diagnostic accuracy. It's probably worth making that clear by presenting the sensitivity and specificity values for the tests you are comparing using references to a large study or review. This would clear the reader's mind and refocus it on the question addressed here. In addition, it would be useful to more explicitly mention the outcomes studied here (referral for ICA/ number of revascularizations etc.).**

Reply: Thank you or pointing to this issue. Indeed, the aim of the present study was to focus on diagnostic randomized controlled trials and the respective clinical outcomes assessed in these trials. A systematic summary of studies on diagnostic accuracy of the above mentioned diagnostic modalities was beyond the scope of this work, and this aspect has been evaluated previously. Following your recommendation, we have summarized in the following Table, metrics of diagnostic accuracy (sensitivity, and specificity) for coronary artery disease detection for each assessed imaging modality by using invasive coronary angiography as the gold standard. We gave preference to comprehensive meta-analyses, whenever available. We mention in the Results section: "*… The diagnostic accuracy of the evaluated imaging modalities based on previously published studies is shown in Appendix 3. …*". We now provide in Box 2, as response to one of your comments above, definitions for the endpoints of invasive coronary angiography, revascularizations, and overall downstream testing.

Appendix 3: Sensitivity and specificity of each non-invasive diagnostic modality of interest in previously published studies.		
	Sensitivity	**Specificity**
Exercise electrocardiogram (PMID: 27499958)	0.66 (95%CI: 0.59 to 0.72)	0.75 (95%CI: 0.71 to 0.79)
Stress echocardiography (PMID: 23074412)	0.80 (95%CI: 0.77 to 0.82)	0.84 (95%CI: 0.82 to 0.87)
Single-photon emission computed tomography – myocardial perfusion imaging (PMID: 25596143)	0.61 (95%CI: 0.56 to 0.66)	0.84 (95%CI: 0.81 to 0.87)
Real-time myocardial contrast echocardiography (PMID: 23770168)	0.75 (95%CI: 0.69 to 0.82)	0.52 (95%CI: 46 to 59)
Coronary computed tomographic angiography (PMID: 25596143)	0.78 (95%CI: 0.72 to 0.82)	0.86 (95%CI: 0.83 to 0.88)
Cardiovascular magnetic resonance (PMID: 25596143)	0.87 (95%CI: 0.84 to 0.90)	0.91 (95%CI: 0.89 to 0.92)

Comment: *** The included RCTs are in a separate reference list, which is not helpful. Please include in the main reference list.**

Reply: As suggested, we have merged the reference list of the included trials with the main reference list of the manuscript.

<u>Comment:</u> In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

<u>Reply:</u> Below we provide detailed replies to each of the Reviewers' comments.

Comments from Reviewers

Reviewer: 1

Siontis et al performed an impressive and important meta-analysis on the role of functional and anatomical imaging in patients with suspected low-risk acute coronary syndromes (ACS) and stable coronary artery disease (CAD). The 3 most important findings are:
1) In suspected ACS, functional testing reduces ICA, revascularization and costs.
2) In suspected stable CAD, functional testing reduces ICA and revascularization.
3) "…the geometry of our networks of trials suggests that each technological innovation became the standard for trials of future innovations (i.e. CCTA), although no clear advantage in terms of clinical outcomes had been shown compared with previous diagnostic strategies."

Reply: Thank you for this positive comment.

Comment: My suggestions to improve the manuscript for the general reader are as follows:
The British Medical Journal is read by physicians from many different specialties, not just experts in statistics or meta-analyses. The abstract and certain parts of the manuscript are difficult to read. Therefore, I would suggest to keep definitions and conclusions precise and simple. For example, according to the title of the manuscript, the goal of the current study is to assess outcome related to the results of a certain imaging test which detects or excludes ischemia/stenosis. Thus, the goal of the study would be "outcome in terms of the number of invasive coronary angiographies, death, myocardial infarction after a positive or negative test result" and not "efficacy of modalities for detection of coronary artery disease (significant =hemodynamically relevant stenosis?) " The latter would require a gold standard such as FFR.

Reply: We wish to thank the Reviewer for the important comment. We have now revised the corresponding sentences in Abstract and Introduction as follows: Abstract-Objective: "*Objective: To evaluate differences in downstream testing, coronary revascularization and clinical outcomes following non-invasive diagnostic modalities for coronary artery disease detection.*" and in Introduction: "*… To date, diagnostic randomized controlled trials do not provide conclusive evidence as to whether a noninvasive anatomical or functional testing strategy provides the most favorable results in terms of subsequent downstream testing or relevant clinical outcomes. We therefore summarized the available evidence and evaluated clinical endpoints of different noninvasive diagnostic modalities in patients with symptoms suggestive of coronary artery disease through network meta-analysis.* …". Finally, following the recommendation of the Editors, we provide definitions of key terms in Box 1 and Box 2.

The abstract is difficult to read:
Comment: 1) relative efficacy. As described above, what is meant by this term? Efficacy to diagnose "obstructive CAD"? Then there would be a need for a gold

standard within each study included. The number of ICA following the initial test? The safety regarding outcome? Please give a clear definition for a general reader.

Reply: Thank you for raising this important issue. Our aim was not to evaluate the diagnostic performance (diagnostic accuracy) of different diagnostic modalities to appropriately diagnose relevant coronary artery disease, but to evaluate the impact of each diagnostic test on downstream testing (in terms of referrals for invasive coronary angiography and overall testing), coronary revascularization rates and associated clinical outcomes.

Therefore, there was no need to define the gold standard reference test in each study, as would have been the case if we had been evaluating the diagnostic accuracy of each diagnostic modality. Moreover, the resulting networks of diagnostic interventions for both study populations (low-risk acute coronary syndrome and stable coronary artery disease patients) suggest that each technological innovation (e.g. coronary computed tomographic angiography) became the standard comparator for trials of future innovations.

Apart from the above-mentioned revisions, we have also included additional changes aiming to simplify the text in the Abstract. All changes are highlighted in the revised version of the manuscript.

Comment: 2) downstream testing favored a diagnostic strategy with stress echo. What is meant by downstream testing is favoring something? ICA after an initial SPECT is downstream testing or a CT after initial exercise-ECG is downstream testing. This second testing favored a certain first test?

Reply: Thank you for this comment and we acknowledge that this wording may have been confusing. As "downstream testing", we considered any additional test required following the initial diagnostic modality of interest (one of the diagnostic test comparators in individual diagnostic randomized controlled trials).

We now provide a short description of such key terms used thorough the manuscript in Box 1. The sentence in the Abstract has been revised as follows: "… *In patients with suspected stable coronary artery disease, an initial diagnostic strategy with stress echocardiography or single-photon emission computed tomography-myocardial perfusion imaging resulted in fewer downstream tests compared with a strategy of coronary computed tomographic angiography (odds ratio of 0.24 (0.08-0.74) and 0.57 (0.37-0.87) respectively); whereas exercise electrocardiogram yielded the highest downstream testing rate.* …".

We would also like to clarify, that we considered the number of invasive coronary angiography referrals as an indicator of downstream testing on the basis of the hypothesis that a non-invasive anatomical-driven diagnostic strategy may be more sensitive to identify clinically relevant coronary artery disease (based on previously published evidence) which in turn may have a prognostic impact.

Comment: 3) the estimates cannot rule out a significant impact on clinical outcomes associated with individual tests. Please simplify this sentence. In addition, it is more a result than a conclusion. It is somehow contradictory to the

conclusion section of the manuscript which states the same risk in ACS-patients for functional or anatomical.

Reply: Thank you for noticing this. We have now revised the conclusion in the Abstract as follows: "*Conclusions: In low-risk acute coronary syndrome patients, an initial diagnostic strategy using stress echocardiography or cardiovascular magnetic resonance is associated with fewer referrals for invasive coronary angiography and revascularization procedures compared with anatomical testing, without apparent impact on future risk of myocardial infarction. Among patients with suspected stable coronary artery disease, there was no clear discrimination between individual diagnostic strategies regarding the subsequent need for invasive coronary angiography, and differences in terms of the risk of myocardial infarction cannot be ruled out.*".

Comment: 4) Please state what types of imaging tests were included/assessed: SPECT, MR, echo, X-ECG, CT.

Reply: We now mention in the Abstract: "…. *Data synthesis: We performed a random-effects network meta-analysis to synthesize available evidence from diagnostic randomized controlled trials evaluating the effect of non-invasive diagnostic modalities (exercise electrocardiogram, stress echocardiography, single-photon emission computed tomography-myocardial perfusion imaging, real-time myocardial contrast echocardiography, coronary computed tomographic angiography, cardiovascular magnetic resonance) on downstream testing and patient-oriented outcomes. ….*".

Comment: 5) Eligibility criteria: instead of under "different clinical settings" "under two different clinical settings"

Reply: The sentence has been revised as follows: "*Eligibility criteria for selecting studies: Diagnostic randomized controlled trials comparing non-invasive diagnostic modalities for coronary artery disease detection in patients presenting with symptoms suggestive of low-risk acute coronary syndrome or stable coronary artery disease.*".

Please make changes accordingly in the manuscript.

Reply: This has been done as appropriate.

Introduction/Objective:
Comment: Needs clarifying. Please state with simple words what the study aims and objectives were. What was the idea behind the manuscript initially before the results were available? E.g. anatomical testing is not better than functional? In case of stable CAD, the promise-trial already showed no difference between functional and anatomical testing.
Please explain again what is meant by relative efficacy.

Reply: Thank you for this comment. Please also note our reply to the comment of the Editors on the novelty of our findings. We now mention in the Introduction: "… *Although the American College of Cardiology Foundation/American Heart Association guidelines published in 2012 recommended the use of functional testing based mainly on evidence derived from studies of diagnostic accuracy (as the vast majority of diagnostic randomized trials were published after these guidelines)*[11]*, recent audits in large numbers of patients showed only a modest impact on subsequent diagnostic findings.*[12] …", and "…. *To date, diagnostic randomized controlled trials do not provide conclusive evidence as to whether a noninvasive anatomical or functional testing strategy provides the most favorable results in terms of subsequent downstream testing and relevant clinical outcomes. We therefore summarized the available evidence and evaluated clinically relevant endpoints of different noninvasive diagnostic modalities in patients with symptoms suggestive of coronary artery disease through network meta-analysis.* …".

Methods:

Comment: What is the definition of low-risk ACS in the manuscript (I might got lost somewhere between the impressive 207 pages of the total manuscript.)? It seems to be defined only in the discussion section as patients with suspected ACS without relevant ECG-changes and negative biomarkers. However, there has been a shift of paradigm at least during the last 5 years in ACS since the introduction of high sensitive troponine T assays: A negative high sensitive troponine T means that there is no ACS and subsequent imaging or exercise-ECG are not required anymore. A positive hsTNT, however, does not necessarily say it is always a coronary problem (Tachycardia, low blood pressure/perfusion, renal function impairment etc. may result in elevated levels of hsTNT). In this group of patients with non-diagnostic ECG and positive hsTNT imaging could reduce the number of unnecessary ICA. Please define ACS in the method section and discuss whether imaging in ACS and the findings of the manuscript for ACS are still relevant in the era of hsTNT.

The study with the largest number of patients from Lim et aliter seemed to include mostly patients without ACS since all patients with positive troponines or slight ECG-changes were excluded ("Only participants who had a negative 6-hour observation received their randomly assigned protocol.").

Reply: Thank you for highlighting this critical point. In the new display item of our manuscript "Box 1" (please see above) we now provide the definition of the low-risk acute coronary syndrome population which was adopted with minor differences among the included diagnostic randomized controlled trials: "*Low-risk acute coronary syndrome patients: Patients typically presenting with chest pain (or anginal equivalent) of at least 5 minutes duration at rest within the last 24 hours, without history of known coronary artery disease, without diagnostic ischemic changes on the electrocardiogram, without hemodynamic or clinical instability, and an initial troponin level lower than the 99th percentile of the used assay. This group of patients typically does not require immediate assessment by invasive coronary angiography.*".

We fully agree with your statement. The authors of 3 out of 18 diagnostic randomized controlled trials of low-risk acute coronary syndrome patients reported the use of a high sensitive troponin assays. However, the key point of appropriate use of high sensitive cardiac troponin assay is the appropriate selection of patients presenting

in the emergency department. As has been recently shown (Shah et al. BMJ 2017), diagnostic testing without appropriate patient selection, results in a very low prevalence of type 1 myocardial infarction and a low positive predictive value of an elevated cardiac troponin concentration for type 1 myocardial infarction. On the other hand, appropriate diagnostic testing in those patients with a higher pre-test probability, considerably increases the positive predictive value of high sensitivity cardiac troponin. When high sensitivity cardiac troponin testing is widely performed or used without previous clinical assessment, elevated troponin concentrations are common and predominantly reflect myocardial injury rather than type 1 myocardial infarction (Shah et al. BMJ 2017). Consequently, the wide use of high sensitivity cardiac troponin assays has resulted in increased frequency of type 2 myocardial infarction or myocardial injury, potentially leading to diagnostic uncertainty and unnecessary subsequent investigations of patients without acute coronary syndrome. We now mention in Results: "… *Only in three[41,43,46] out of the 18 trials of low-risk acute coronary syndrome patients the authors clarified the use of a high sensitive troponin assay.* …".

Finally, we mention in Discussion "… *In our meta-analysis, a diagnostic strategy based on anatomical-testing with use of coronary computed tomographic angiography was associated with increased referral rates for downstream invasive coronary angiography and revascularization, some of which may have occurred in the absence of evidence of ischemia. High sensitivity troponin assays, which were used in a minority of the included trials in our meta-analysis, are nowadays available and negative test results can serve as an efficient gatekeeper of unnecessary downstream diagnostic testing in this group of patients. However, noncoronary diseases may also cause elevated high sensitivity troponin levels and subsequently subject patients with low pre-test probability for coronary artery disease to unnecessary interventions. Therefore, the selection of patients with a higher pre-test probability presenting in the emergency department, the definition of higher initial cutoff values and the focus on dynamic changes over time are key points of the appropriate diagnostic testing in this clinical setting by increasing the positive predictive value of high sensitivity cardiac troponin.(Shah et al. BMJ 2017). In our analysis, the rate of clinical events was low and our estimates are therefore imprecise for risk estimates of myocardial infarction, and with wide 95% confidence intervals cannot rule out relevant increases or reductions in the risk of myocardial infarction associated with functional testing.* …".

Results

Comment: Exercise-ECG needs to be mentioned in abstract and it's results and role more described in the manuscript (results, discussion) since it is the most often performed test in many countries.

Reply: We now mention in Abstract: "…. *Among low-risk acute coronary syndrome patients, stress echocardiography, cardiovascular magnetic resonance and exercise electrocardiogram resulted in fewer invasive coronary angiography referrals compared with coronary computed tomographic angiography (odds ratio 0.28 (95%CI 0.14 to 0.57), 0.32 (0.15 to 0.71) and 1.89 (1.0 to 3.58) respectively); there was no impact on the subsequent risk of myocardial infarction, but estimates were imprecise.* …." and "…*In patients with suspected stable coronary artery disease, an initial diagnostic strategy with stress echocardiography or single-photon emission computed tomography-myocardial perfusion imaging resulted in fewer downstream tests compared with a strategy of*

coronary computed tomographic angiography (odds ratio of 0.24 (0.08-0.74) and 0.57 (0.37-0.87) respectively); whereas exercise electrocardiogram yielded the highest downstream testing rate.…". We have also further commented on exercise electrocardiogram in Results and Discussion (changes are highlighted). The respective indirect estimates are provided in the main Figures of the manuscript, and detailed Results are available as supplementary material.

Discussion

The main questions seem to be whether

<u>Comment:</u> 1) the presence of non-obstructive coronary artery disease - which could only be detected by CT and not by MR / SPECT / PET / stress-echo / exercise ECG - leads to an impaired prognosis if not treated with medication. In a single randomized study, this question already has been answered by the large Promise-trial (N Engl J Med 2015; 372:1291) showing no difference between CT and the other modalities.

<u>Reply:</u> Thank you for highlighting this issue. Indeed, non-obstructive coronary artery disease can only be detected with coronary computed tomographic angiography or with invasive coronary angiography. The clinical significance of such non-obstructive coronary lesions detected by invasive or non-invasive coronary angiography remains under question.

The detection of "non-significant" lesions has become common nowadays by the widespread use of non-invasive anatomical testing, and is considered a condition requiring medical therapy. However, this perception of "innocent" non-obstructive coronary artery disease may be incorrect, since prior studies have noted that the majority of plaque ruptures and subsequent myocardial infarctions arise from such non-obstructive coronary lesions (Libby P., et al. Circulation 2005; Shah PK., et al. Curr Opin Lipidol 2007; Ambrose JA., et al. JACC 1988; Falk E., et al. Circulation 1995). The ability to explore clinical outcomes among patients with non-obstructive coronary artery disease has been limited by insufficient data about both the clinical condition and its related outcomes, since the majority of the studies in coronary artery disease have been limited to patients with obstructive coronary artery disease. In a large-scale retrospective cohort of patients undergoing elective coronary angiography (Maddox T., et al. JAMA 2014), the presence of non-obstructive coronary artery disease (detected in 8,384 patients), compared with no apparent coronary artery disease, was associated with a significantly greater 1-year risk of myocardial infarction and all-cause mortality; whereas 50-60% of the study population with non-obstructive coronary artery disease received therapy with statin/β-blockers/ACEIs-ARBS after the diagnostic coronary angiogram. Another study (Bittencourt MS., et al. Circ Card Imaging 2014) focusing on the presence of non-obstructive coronary artery disease detected by coronary computed tomographic angiography concluded that the extent of non-obstructive coronary lesions is associated with increased risk of future cardiovascular events, with a hazard ratio of 3.1 (95%CI 1.5-6.4) for the presence of extensive non-obstructive coronary artery disease. In a recently published nationwide register (Jørgensen ME., et al. JACC 2017), patients with stable symptoms who underwent initial noninvasive anatomical cardiac imaging (coronary computed tomographic angiography) were more likely to receive medical therapy (in terms of statin therapy and antihypertensives) and undergo invasive coronary assessment and subsequent revascularization compared to

the patient who underwent assessment with functional testing; while the authors found that patients who underwent coronary computed tomographic angiography had a 29% lower risk of myocardial infarction.

The above findings should be interpreted with caution and should be used only to formulate a research hypothesis and not derive definite conclusions, since they have been derived from non-randomized retrospective studies (with well-known inherited limitations) and have not been validated in any of the landmark diagnostic randomized controlled trials that examined the role of coronary computed tomographic angiography for the assessment of patients suspected of stable coronary artery disease (PROMISE and SCOT-HEART). Moreover, none of the above studies addressed the question whether it was the intensive medical therapy (primary/secondary prevention) of coronary artery disease, or the increased invasive coronary testing and subsequent revascularization, or both, which subsequently impacted the risk of myocardial infarction.

We have now modified the relevant part of the Discussion as follows: "… *In a nationwide cohort study, Jorgensen et al found a diagnostic approach based on non-invasive anatomical testing to be associated with modifications to cardiovascular-related medications, increased downstream invasive coronary testing and subsequent revascularization, and a lower risk of myocardial infarction (hazard ratio 0.71, 95%CI 0.61-0.82) compared with functional testing.*[79] *Similarly, a conventional meta-analysis including three trials in the corresponding analysis showed a borderline significant reduction of myocardial infarction with coronary computed tomographic angiography compared to a mixture of functional testing and standard care (odds ratio 0.69, 95%CI 0.49 to 0.98).*[80] *In our network meta-analysis, we found a statistically non-significant signal of a similar magnitude. Results in Figure 3 – Panel B correspond to an odds ratio of myocardial infarction of 0.74 favoring coronary computed tomographic angiography over functional testing (95%CI 0.48 to 1.15). However, our network meta-analysis made full use of all available evidence from 12 randomized trials comparing 7 different diagnostic strategies within a single analysis, appropriately quantifying the uncertainty of hard clinical outcomes associated with these strategies. Nevertheless, both direction and magnitude of the effects found in our analysis are comparable with the large cohort study by Jorgensen et al*[79] *and the conventional meta-analysis*[80]*. A decrease in the risk of subsequent myocardial infarction related to an anatomical testing strategy is indeed possible and cannot be ruled out based on our results. However, whether intensification of medical therapy (primary/secondary prevention) or the increased rate of subsequent revascularization, or both, impact on the prognosis of patients undergoing coronary computed tomographic angiography remains to be clarified. Finally, the baseline risk of myocardial infarction in the landmark PROMISE trial and the cohort study by Jorgensen et al were low (0.6% and 0.8% up to 1 month respectively), resulting in absolute differences in the risk of myocardial infarction between functional testing and coronary computed tomographic angiography of approximately 0.2%, with a corresponding number-needed-to-harm around 500 for this outcome (Table 2), which is arguably irrelevant to raise safety concerns.* …".

<u>Comment:</u> 2) the investigation of low risk groups leads to measurable differences between different imaging modalities.

Reply: This is a key point for the future research agenda. Randomised clinical trials, in our case diagnostic randomised clinical trials, have rapidly evolved as a mainstay of evidence-based clinical medicine. Nonetheless, their reliability, validity, and generalizability strongly depend on the methodologic rigor implemented to obtain results and draw robust conclusions. Performance of sample size calculation for an appropriate primary end point is an essential step in this process that should be completed before initiating the trial. Concurrent treatment and follow-up of subjects randomly allocated to experimental and control groups is not only one of the key features that has led us to adopt RCTs as the gold standard evaluation tool but can also be a caveat when patients are doing "too well" and low event rates compromise the assumptions made in the sample size calculation. Although overestimation of event rates does not seem to be uncommon, this can have a detrimental impact on the power of a randomised trial. When event rates are low, the use of composite endpoints with broader definitions allows investigators to reduce sample size and the duration of follow-up. However, these advantages come at a price: since the interpretation of the effect may be complicated and the composite endpoint can be profoundly misleading.

We mention in Discussion: "…. *Our systematic evaluation showed that the low event rates have resulted in sample sizes of thousands of patients in recent trials but without allowing for a clear discrimination between the individual diagnostic strategies. Along the same lines, the use of broader clinical (composite) endpoints might be clinically meaningful in future trials. More important, the geometry of our networks of trials suggests that each technological innovation became the standard for trials of future innovations (i.e. coronary computed tomographic angiography), although no clear advantage in terms of clinical outcomes had been shown compared with previous diagnostic strategies. Future adequately powered clinical trials should aim to clarify the differential effects on more broadly defined clinical outcomes (which may occur during longer follow-up periods), and subsequent use of hospital resources and cost-effectiveness aspects of the implemented strategies, which are representative of current clinical practice.* ….".

Comment: Please also discuss the endpoints: ICA and revascularization are potentially physician-driven outcome parameters whereas death and myocardial infarction are not.

Reply: Thank you - this is an important point and we now articulate the limitation clearly in the Discussion/Limitations: "… *Forth, the primary endpoints of invasive coronary angiography and revascularization is partially attributed to physician judgment, which is not the case for the patient-oriented outcomes of death and myocardial infarction….*".

Comments: What are the suggestions of the authors regarding a potential significant impact on clinical outcomes? It seems to be irrelevant? If so, perform exercise ECG in all patients able to exercise (The number of downstream tests after exercise ECG is mostly driven by the number of non-diagnostic tests due to inability to exercise?)?

Reply: Regarding the potential significant impact of diagnostic testing on clinical outcomes in the group of patients with suspected stable coronary artery disease, we refer to our previous answers to your comments above. Regarding the impact of diagnostic testing on clinical outcomes in the group of low-risk acute coronary syndrome patients: we mention in Discussion that "… *In our analysis, the rate of clinical events was low and our estimates are therefore imprecise for risk estimates of myocardial infarction, and with wide 95% confidence intervals cannot rule out relevant increases or reductions in the risk of myocardial infarction associated with functional testing.* …". Please also consider our reply above on the low event rate.

We did not find any difference between exercise electrocardiogram compared to coronary computed tomographic angiography for all the examined outcomes, apart from overall downstream testing in patients presented with symptoms suggestive of stable coronary artery disease. In our network meta-analysis, an initial diagnostic strategy with coronary computed tomographic angiography resulted in less additional diagnostic testing compared to exercise electrocardiogram. Indeed, this can be attributed to higher percentage of non-diagnostic or non-specific changes during the test. Following your comment regarding inability to exercise, we went back to the respective reports the trials, but this information was not provided.

Comment: * Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.
Yes
1) In suspected ACS, functional testing reduces ICA, revascularization and costs.
2) In suspected stable CAD, functional testing reduces ICA and revascularization.
3) "… the geometry of our networks of trials suggests that each technological innovation became the standard for trials of future innovations (i.e. CCTA), although no clear advantage in terms of clinical outcomes had been shown compared with previous diagnostic strategies."

Reply: Thank you for your positive comment.

Comment: * Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it? Not in its current version: this needs to be improved by a revision.

Reply: The current version has been considerably revised towards this direction.

Comment: * Scientific reliability
Research Question - clearly defined and appropriately answered?
Yes
Overall design of study - adequate ?
Yes

Reply: Thank you for your positive comment.

Comment: **Participants studied - adequately described and their conditions defined?**
A better definition of ACS is needed.
Low risk-groups were studied.

Reply: The definition of low-risk acute coronary syndrome patients is now provided in Box 1 of the revised manuscript.

Comment: **Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?**
Yes

Reply: Thank you for your positive comment.

Comment: **Results - answer the research question? Credible? Well presented? Credible.? Research question not fully answered: No impact on risk of myocardial infarction, but estimates were imprecise?**

Reply: This is correct. We clarify this in Discussion section.

Comment: **Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?**
Yes

Reply: Thank you for your positive comment.

Comment: **References - up to date and relevant? Any glaring omissions?**
hsTNT paradigm shift in ACS-patients is missing

Reply: We have revised the Discussion with specific referral to high sensitive troponin assays and their role in appropriate patients selection required subsequently testing. The following recently published study has been cited: "Shah ASV., et al. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. BMJ. 2017;359:j4788. doi: 10.1136/bmj.j4788."

Comment: **Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?**
Abstract and objectives need clarifying. The abstract is difficult to read.

Reply: Following your suggestion and comments above, we have considerably revised the Abstract. We hope now it has been considerably improved and it is appropriate in the current form for the general medical community of the BMJ.

ABSTRACT:

Objective: To evaluate differences in downstream testing, coronary revascularization and clinical outcomes following non-invasive diagnostic modalities for coronary artery disease detection.
Design: Systematic review and network meta-analysis of diagnostic randomized controlled trials.
Data sources: Medline, Medline in process, Embase, Cochrane Library for clinical trials, Pubmed, Web of Science, SCOPUS, WHO International Clinical Trials Registry Platform, and Clinicaltrials.gov.
Eligibility criteria for selecting studies: Diagnostic randomized controlled trials comparing non-invasive diagnostic modalities in patients presenting with symptoms suggestive of low-risk acute coronary syndrome or stable coronary artery disease.
Data synthesis: We performed a random-effects network meta-analysis to synthesize available evidence from trials evaluating the effect of non-invasive diagnostic modalities (exercise electrocardiogram, stress echocardiography, single-photon emission computed tomography-myocardial perfusion imaging, real-time myocardial contrast echocardiography, coronary computed tomographic angiography, cardiovascular magnetic resonance) on downstream testing and patient-oriented outcomes in patients with suspected coronary artery disease. Unpublished outcome data were obtained from 11 trials.
Results: We included 30 diagnostic randomized controlled trials (18 trials with 11,329 low-risk acute coronary syndrome patients and 12 trials with 22,062 patients with suspected stable coronary artery disease). Among low-risk acute coronary syndrome patients, stress echocardiography, cardiovascular magnetic resonance and exercise electrocardiogram resulted in fewer invasive coronary angiography referrals compared with coronary computed tomographic angiography (odds ratio 0.28 (95%CI 0.14-0.57), 0.32 (0.15-0.71) and 1.89 (1.0-3.58) respectively); there was no impact on the subsequent risk of myocardial infarction, but estimates were imprecise. Heterogeneity and inconsistency were low. In patients with suspected stable coronary artery disease, an initial diagnostic strategy with stress echocardiography or single-photon emission computed tomography-myocardial perfusion imaging resulted in fewer downstream tests compared with a strategy of coronary computed tomographic angiography (odds ratio of 0.24 (0.08-0.74) and 0.57 (0.37-0.87) respectively), whereas exercise electrocardiogram yielded the highest downstream testing rate. The estimates were imprecise without clear discrimination between the individual strategies for death and myocardial infarction.
Conclusions: In low-risk acute coronary syndrome patients, an initial diagnostic strategy using stress echocardiography or cardiovascular magnetic resonance is associated with fewer referrals for invasive coronary angiography and revascularization procedures compared with anatomical testing, without apparent impact on the future risk of myocardial infarction. Among patients with suspected stable coronary artery disease, there was no clear discrimination between individual diagnostic strategies regarding the subsequent need for invasive coronary angiography, and differences in terms of the risk of myocardial infarction cannot be ruled out.
Systematic review registration: This study is registered with PROSPERO (CRD42016049442).

Reviewer: 2

Comment: **In the present study the authors performed a comprehensive meta-analysis of RCTs evaluating the use of non-invasive testing for the assessment of CAD and its relationship with patient outcomes.**
The subject is of great clinical relevance and the manuscript is well written. However, there are several issues that are reason for concern and, therefore, requires further discussing.

Reply: We thank the reviewer for his positive comment on our manuscript. We have attempted to address his concerns below and revised the manuscript accordingly.

Comment: 1- The main issue is related to the general message conveyed by the paper. Even though the authors did exercise some care when they phrased the conclusion of the manuscript, the general message of the paper could be summarized as follows: (a) The CCTA strategy is associated with higher rates of ICA referrals and revascularizations; (b) However, it is not associated with lower rates of MI and/or death; (c) Hence, the "excess" ICAs and revascularizations associated with the CCTA strategy are not beneficial and represented, at the least, a waste of resources; (d) Therefore, the strategy of using CCTA is worse than the strategies based on functional assessment modalities.

This general message can be exemplified by the following segments of the Discussion Section:
"A functional testing strategy may provide important cost benefits owing to fewer referrals for ICA and revascularization and lower radiation and contrast agent exposure while resulting in similar clinical outcomes" (page 20). and
"For outpatients with suspected stable angina, our comprehensive synthesis of D-RCTs indicates that an initial strategy based on functional testing may be valuable in the diagnostic work-up, resulting in fewer referrals for ICA and revascularization" (page 20). and
"US guidelines published in 2012, recommend functional testing as the initial strategy… Our results are in agreement with these guidelines but in contradiction with the recently updated National Institute for Health and Care Excellence (NICE) guidelines, which advise an anatomical based-approach (CCTA) as first line diagnostic strategy…" (page 21).

I do not agree with this way of interpreting the data that was presented. Ultimately, for this rationale to make sense, the fundamental premise is that the CCTA strategy is not associated with lower rates of MI and/or death. So let's look into that in greater detail.
In the present study the authors state that "None of the diagnostic strategies had an impact on the subsequent risk of myocardial infarction, although estimates were imprecise". However, as also mentioned by the authors, a previous meta-analysis (Bittencourt et al. Circ Cardiovasc

Imaging. 2016 Apr;9(4)) and a very large cohort study (Jorgensen et al. J Am Coll Cardiol 2017;69:1761–70) demonstrated a significant reduction of MI rates with the CCTA strategy in patients with stable CAD. So, are the results of the present study in agreement or in contrast with these previous reports? The general message conveyed by the authors assumes that their findings are in contrast with the abovementioned previous studies. I do not see it that way.

The present study clearly showed a trend towards MI reduction with the CCTA strategy among patients with suspected stable CAD. Indeed, the point estimate of the present study comparing CCTA versus functional testing (0.74 [0.48-1.15]) was very similar to the point estimates of the previous meta-analysis by Bittencourt et al. (0.69 [0.49-0.98]) and the previous study by Jorgensen el al. (0.71 [0.61-0.82]). The difference is that in the present study the CIs were wider and, therefore, the p-values were statistically non-significant. The reason for the wider CIs is most likely the fact that the present meta-analysis included a larger number of RCTs that were more different from one another. This resulted in a higher degree of heterogeneity (not only heterogeneity that is statistically quantifiable, but equally as important, conceptual heterogeneity) and, as a consequence, a higher degree of imprecision (Mills et al. BMJ 2013;346:f2914), which is mentioned several times throughout the manuscript. Therefore, by using a network meta-analysis that included a larger number of RCTs the authors gained the advantage of being able to look at a bigger picture regarding the use of non-invasive testing for the assessment of stable CAD. However, this advantage was obtained at the expense of study precision (resulting in wider CIs).

So, when we put the findings of the present study into context, taking into consideration the results of the abovementioned previous studies, it seems much more reasonable to conclude that there is robust evidence that the CCTA strategy is, in fact, associated with lower rates of MI in patients with stable CAD. I believe the authors put too much emphasis on the statistically non-significant p-value instead of looking into the bigger picture.

<u>Comment:</u> 2- Moreover, if we consider that there is robust evidence that CCTA strategy is associated with lower rates of MI, then the authors would have to review their interpretation regarding the outcomes of ICA referrals and revascularization. As mentioned previously, the general message of the paper is based on the concept that these are "negative" outcomes. However, based on the previous discussion, this is most likely not the case. If the CCTA strategy results in lower rates of MI, then it would make more sense to consider the possibility that the higher rates of ICA and revascularizations were, in fact, "positive" outcomes that contributed to the lower rates of MI.
In this context, it would be very informative if the authors could provide data that could help us determine whether these ICAs and revascularization referrals were "appropriately" indicated or not. For

example, it would allow us to get a clearer picture about this issue if the authors could provide data regarding the proportion of ICAs showing normal coronary arteries or only non-significant (<50%) CAD within each non-invasive test modality.

Reply to comments 1 and 2: We wish to thank the reviewer for the above thoughtful and constructive comments. We have extensively revised the manuscript in an effort to make our findings clear to a broader audience.

Several critical issues emerged by reviewing the summary of the available diagnostic randomized controlled trials in stable coronary artery disease imaging. The follow-up time window for the clinically oriented outcomes in these reported trials was quite short, meaning that longer-term outcomes could not be comprehensively evaluated. In addition to the clinical endpoints, the recent D-RCTs often enrolled lower-risk patients resulting in lower rates of clinical outcomes. This is particularly problematic in combination with the short follow-up period chosen in these trials. The preponderance of neutral ("negative") trials in the field may indicate weaknesses in trial design, target study population, or other factors that uniquely impact cardiovascular imaging. Although it can be argued that this is representative of the current population undergoing testing for suspected stable coronary artery disease, it may not reflect appropriate test populations, and the reported lower-risk findings prompt consideration of alternative trial designs and statistical approaches (e.g., reduced effect size, smaller alpha, higher beta levels, larger standard deviation estimates, and broader definitions of clinical outcomes). We mention in the Discussion: "… *Future adequately powered clinical trials should aim to clarify the differential effects on more broadly defined clinical outcomes (which may occur during longer follow-up periods), and subsequent use of hospital resources and cost-effectiveness aspects of the implemented strategies, which are representative of current clinical practice.* …".

Of note, important considerations emerge from the PROMISE and SCOT-HEART trials, both landmark trials in the current field, which can serve as a platform for future trial design. The overall cardiac-death or myocardial infarction rates observed in SCOT-HEART were >2-fold higher than for the PROMISE trial, as they enrolled a higher-risk cohort. Based on this and given the borderline effect size in SCOT-HEART (HR: 0.62; 95%CI 0.38 to 1.01; p=0.053), one may hypothesize whether coronary computed tomographic angiography may prove beneficial in a cohort with more prevalent coronary artery disease. The prevalence of obstructive coronary artery disease was 42.0% for SCOT-HEART but only 11.9% for PROMISE, as detected by coronary computed tomographic angiography. Appropriate patient group selection, with higher coronary artery disease prevalence, would result more patients requiring the use of primary/secondary prevention and anti-ischemic therapies with established effectiveness.

We appropriately caution that our data cannot rule out a significant benefit in terms of myocardial infarction reduction and we summarize this as follows: "*Neither functional nor non-invasive anatomical testing have an apparent impact on the subsequent risk of myocardial infarction; nevertheless the estimates for both groups cannot rule out a significant impact on clinical outcomes associated with individual tests and requires further study.*". We now mention in

Discussion: "… *A decrease in the risk of subsequent myocardial infarction related to an anatomical testing strategy is indeed possible and cannot be ruled out based on our results. However, whether the optimization of medications towards enhanced primary/secondary prevention of cardiovascular disease or the subsequent revascularization, or both, impact the prognosis of patients undergo coronary computed tomographic angiography remains to be clarified. Finally, the baseline risk of myocardial infarction in the landmark PROMISE trial and the cohort study by Jorgensen et al were low (0.6% and 0.8% up to 1 month respectively), resulting in absolute differences in the risk of myocardial infarction between functional testing and coronary computed tomographic angiography of approximately 0.2%, with a corresponding number-needed-to-harm around 500 for this outcome (Table 2), which is arguably irrelevant to raise safety concerns.* …".

As we showed in our comprehensive analysis, there was definitely greater resource utilization with coronary computed tomographic angiography compared to what was considered in the randomized trials as "standard of care", without proof of clinical benefit. We would like to clarify that we provide downstream invasive coronary angiography neither as a "negative" nor as a "positive" outcome, but as an indicator of downstream testing based on the hypothesis that a non-invasive anatomically driven strategy may be more sensitive to identify non-clinically significant coronary artery disease and subsequently may have a prognostic impact. Overall, the findings derived from non-randomized retrospective cohorts (i.e. Jorgensen et al., JACC 2017 and others mentioned above) show that a non-invasive anatomical-based diagnostic strategy has an impact on subsequent medical therapy (implementation of medical therapy towards more aggressive primary/secondary prevention in case of obstructive/non-obstructive coronary artery disease or discontinuation of cardiovascular-related medications in case of normal findings), increases the rate of invasive coronary angiography and subsequent revascularizations, and may have a positive impact on the subsequent risk of myocardial infarction. Nevertheless, the latter finding has not been validated in the landmark diagnostic randomised controlled trials that examined the role of coronary computed tomographic angiography for the assessment of patients with suspected stable coronary artery disease (PROMISE and SCOT-HEART). Of note, none of the above mentioned studies was designed to address whether intensification of medical therapy towards secondary prevention of coronary artery disease, or increased invasive coronary testing and subsequent revascularization, or both following a specific non-invasive diagnostic strategy have an impact on the subsequent risk of myocardial infarction. We provide above a detailed answer to a similar comment.

As mentioned, we have now modified the relevant part of the Discussion as follows: "…*In a nationwide cohort study, Jorgensen et al found a diagnostic approach based on non-invasive anatomical testing to be associated with modifications to cardiovascular-related medications, increased downstream invasive coronary testing and subsequent revascularization, and a lower risk of myocardial infarction (hazard ratio 0.71, 95%CI 0.61-0.82) compared with functional testing.*[79] *Similarly, a conventional meta-analysis including three trials in the corresponding analysis showed a borderline significant reduction of myocardial infarction with coronary computed tomographic angiography*

compared to a mixture of functional testing and standard care (odds ratio 0.69, 95%CI 0.49 to 0.98).[80] In our network meta-analysis, we found a statistically non-significant signal of a similar magnitude. Results in Figure 3 – Panel B correspond to an odds ratio of myocardial infarction of 0.74 favoring coronary computed tomographic angiography over functional testing (95%CI 0.48 to 1.15). However, our network meta-analysis made full use of all available evidence from 12 randomized trials comparing 7 different diagnostic strategies within a single analysis, appropriately quantifying the uncertainty of hard clinical outcomes associated with these strategies. Nevertheless, both direction and magnitude of the effects found in our analysis are comparable with the large cohort study by Jorgensen et al[79] and the conventional meta-analysis[80]. A decrease in the risk of subsequent myocardial infarction related to an anatomical testing strategy is indeed possible and cannot be ruled out based on our results. However, whether intensification of medical therapy (primary/secondary prevention) or the increased rate of subsequent revascularization, or both, impact the prognosis of patients undergoing coronary computed tomographic angiography remains to be clarified. Finally, the baseline risk of myocardial infarction in the landmark PROMISE trial and the cohort study by Jorgensen et al were low (0.6% and 0.8% up to 1 month respectively), resulting in absolute differences in the risk of myocardial infarction between functional testing and coronary computed tomographic angiography of approximately 0.2%, with a corresponding number-needed-to-harm around 500 for this outcome (Table 2), which is arguably irrelevant to raise safety concerns. …".

As regards to appropriateness of invasive coronary angiography referrals: we fully agree with the importance of this aspect. We went back and reviewed the published reports of the included trials and any relevant information was provided in only 5 out of 30 trials (PMIDs: 27570866, 26746631, 25466568, 22449295, 17320744) with different definitions across the trials in terms of "positive finding" in coronary angiography. Despite the special interest of this aspect, we are not surprised that this information is systematically missing; since the included studies have been designed as randomized controlled trials to evaluate clinical outcomes and not the diagnostic accuracy of each evaluated test. In the latter scenario, the authors would have provided the proportion of invasive coronary angiograms showing normal coronary arteries or only non-significant coronary artery disease within each non-invasive test modality, to be able to calculate diagnostic accuracy metrics.

<u>Comment:</u> 3- At this point, it is important to recognize that a diagnostic test will not reduce the rates of MI and/or death by itself. It will depend on the management decisions that are based on the test results. Moreover, "management" (or "treatment") is not limited to coronary revascularization; it also includes use/adherence of CAD preventive pharmacotherapy and the adoption of positive lifestyle modifications. Indeed, there is evidence that the presence of non-obstructive CAD is associated with increased risk of adverse events, which could be potentially prevented by more aggressive medical therapy (Bittencourt et al. Circ Cardiovasc Imaging. 2014;7:282-291 and Hulten et al. Circ Cardiovasc Imaging. 2014;7:629-638). Moreover, in a sub-study of the

SCOT-HEART trial, Williams et al demonstrated that CCTA "lead to more appropriate use of invasive angiography and alterations in preventive therapies that were associated with a halving of fatal and non-fatal myocardial infarction" (J Am Coll Cardiol 2016;67:1759–68).

Reply: We fully agree with your statement. As we mention above in response to a similar comment of Reviewer 1, a diagnostic test it self will not reduce the risk of future hard clinical outcomes, but will impact on the subsequent medical decisions. To this end, the clinical significance of detection of non-obstructive coronary lesions by invasive or non-invasive coronary angiography is questionable. Nowadays, the detection of such "non-significant" lesions has become common by the widespread of non-invasive anatomical testing, and is considered a condition requiring aggressive medical therapy towards primary/secondary prevention of atherosclerosis progression. However, this perception of "innocent" non-obstructive coronary artery disease may be incorrect, since prior studies have noted that the majority of plaque ruptures and subsequent myocardial infarctions arise from such non-obstructive coronary lesions (Libby P., et al. Circulation 2005; Shah PK., et al. Curr Opin Lipidol 2007; Ambrose JA., et al. JACC 1988; Falk E., et al. Circulation 1995). The ability to explore clinical outcomes among patients with non-obstructive coronary artery disease has been limited by insufficient data about both the clinical condition and its related outcomes, since the majority of the studies in coronary artery disease have been limited to patients with obstructive coronary artery disease. In a large-scale retrospective cohort of patients undergoing elective coronary angiography (Maddox T., et al. JAMA 2014), the presence of non-obstructive coronary artery disease (detected in 8,384 patients), compared with no apparent coronary artery disease, was associated with a significantly greater 1-year risk of myocardial infarction and all-cause mortality; whereas 50-60% of the study population with non-obstructive coronary artery disease received therapy with statin/ β -blockers/ACEIs-ARBS after the diagnostic coronary angiogram. Bittencourt MS., et al. Circ Card Imaging 2014 focused on the impact of the presence of non-obstructive coronary artery disease detected by coronary computed tomographic angiography. In this study, the extent of non-obstructive coronary lesions was associated with increased risk of future cardiovascular events, with a hazard ratio of 3.1 (95%CI 1.5-6.4) for the presence of extensive non-obstructive coronary artery disease. In a recently published nationwide register (Jørgensen ME., et al. JACC 2017), patients with stable symptoms who underwent initial noninvasive anatomical cardiac imaging (coronary computed tomographic angiography) were more likely to receive medical therapy (in terms of statin therapy and antihypertensives) and undergo invasive coronary assessment and subsequent revascularization compared to the patient who underwent assessment with functional testing; while the authors found that patients who underwent coronary computed tomographic angiography had a 29% lower risk of myocardial infarction. The above studies highlight the significance of non-obstructive coronary artery disease detection and the impact of such a diagnostic test on the subsequent therapeutic management. However, the above findings should be interpreted with caution and should be used only to formulate a research hypothesis and not derive definite conclusions, since they have been derived from non-randomized retrospective studies (with well-known

inherited limitations) and have not been validated in any of the landmark diagnostic randomized controlled trials that examined the role of coronary computed tomographic angiography for the assessment of patients suspected of stable coronary artery disease (PROMISE and SCOT-HEART). Moreover, none of the above studies addressed the question whether an intensive medical therapy towards primary/secondary prevention of coronary artery disease, or increased invasive coronary testing and subsequent revascularization, or both subsequently impacted the risk of myocardial infarction.

We have modified the respective section of the Discussion as mentioned above: "… *In a nationwide cohort study, Jorgensen et al found a diagnostic approach based on … number-needed-to-harm around 500 for this outcome (Table 2), which is arguably irrelevant to raise safety concerns.* …".

4- Another important issue is the novelty of the information provided by the present study.

<u>Comment:</u> 4.1- In the beginning of the Discussion Section the authors state:
"This study is the first to assess the available evidence derived from D-RCTs of diagnostic strategies for the detection of CAD in such a systematic and comprehensive way in different clinical settings".
It is widely recognized in the literature that the diagnostic investigation and the therapeutic management are significantly different in patients with suspected low-risk ACS and those with suspected stable CAD. These represent two very different clinical scenarios. Accordingly, in the present study, the authors performed completely separate analyses for these two different clinical settings. In fact, in my opinion, the two analyses could even have been presented in two different papers. I do not see any advantage in putting them together into the same paper.
Having said that, I do not agree that including the analyses of both clinical scenarios into the same paper represent novel information. As we will discuss below, there are several previous meta-analyses investigating these two clinical settings separately.

Reply: Thank you for pointing this out. We considered both clinical settings under the same publication, to capture and provide the whole picture to the readers. We believe that, producing many articles from a moderately sized research project might give it undue significance; whereas splitting the data into segments may also affect the statistical significance of each part and possibly undermine the findings themselves, thus changing an important result into several moderately interesting results. Therefore we decided to include both clinical settings in the same publication, also keeping in mind that we were interested to summarize the available evidence derived from recently published trials. Please see also our reply to your next comment.

<u>Comment:</u> 4.2- The authors also state:
"Among patients with low-risk ACS not required to undergo early invasive assessment, an initial functional diagnostic strategy using stress

echocardiography or CMR was most strongly associated with a reduction in referrals for downstream ICA and revascularization procedures compared with anatomical testing using CCTA".
Here again, the additional novel information is somewhat limited. A previous meta-analysis by Hulten et al (J Am Coll Cardiol 2013;61(8):880-892) demonstrated that CCTA was associated with higher rates of ICA and revascularizations when compared with SOC among low-risk patients with suspected ACS. Another meta-analysis (D'Ascenzo et al. Eur Heart J Cardiovasc Imaging 2013;14:782–789) also demonstrated that CCTA was associated with higher rates of revascularizations.
At this point, I would like to express my concern regarding this particular conclusion. Given that it is based on the comparison of CMR/Echo with CCTA, this conclusion should be interpreted with great caution. First because both CMR and Echo are underrepresented in the network meta-analyses. Second, and most importantly, because there are no direct (head to head) comparisons between either CMR or Echo against CCTA. The comparisons are based exclusively on indirect analyses.

Reply: It is correct that a number of published meta-analyses have addressed these two clinical settings separately. However, we would like to highlight the fact that all previously published meta-analyses are conventional (pairwise) meta-analyses comparing an anatomical-based strategy (based on coronary computed tomographic angiography) versus another single diagnostic approach. A network meta-analysis provides a more concise assessment of the clinical landscape that in turn lends itself better to decision-making.

Through advanced statistical methodology applied in our network meta-analysis, we were able:

- To summarize available evidence of each individual diagnostic test separately and derive indirect estimates for tests comparisons where no evidence from direct comparison exists. We proceeded to quantitative comparisons of such interventions in the absence of head-to-head comparisons in randomized trials.
- To provide an overview of all potential diagnostic strategies examined in diagnostic randomized trials, make full use of the available evidence within a single analysis and subsequently to provide an overall ranking of the available diagnostic strategies.
- To group diagnostic strategies/tests with important similarities, which increased the power of the analysis.
- To combine direct and indirect evidence collectively and enhance the strength of evidence.

Nonetheless, a network meta-analysis is not a substitute for a well conducted randomized controlled trial.

Regarding the previously mentioned conventional meta-analyses: Hulten et al (JACC 2013) included only 4 diagnostic randomized trials on the use of coronary computed tomographic angiography (CCTA) in the emergency department compared to diagnostic intervention labeled "usual care" (which is based on guideline recommendations, locally available technology and expertise, and physicians judgment). Of note, one of the included trials (the CT-STAT trial

by Goldstein JA et al, JACC 2011), did not randomize the patients to CCTA vs. usual care, but to CCTA vs. SPECT-MPI. However, the authors considered this arm of randomization as "usual care". Since then, additional trials have been published. In our network meta-analysis, we included 10 trials including CCTA as comparator. Finally, the authors were not able to provide any information on individual diagnostic tests summarized as usual care. Regarding the meta-analysis of D'Ascenzo et al. (Eur Heart J Cardiovasc Imaging 2013): this is a redundant meta-analysis compared to the previous one, since they included the same 4 trials and assessed the same outcomes. However, they have considered correctly the "control arm" of CT-STAT trial as "SPECT-MPI" and labeled the "control-arm" as "non-CCTA approach".

Comment: **4.3- Finally, the authors also state:**
"Among patients with symptoms suggestive of stable CAD, no clear discrimination was obtained across individual diagnostic strategies for the primary outcome of ICA referrals, mainly because of the limited number of trials contributing to each comparison. Stress echocardiography and SPECT-MPI resulted in less overall downstream testing compared to CCTA. After grouping of widely available functional tests, a functional-testing approach yielded fewer referrals for ICA and subsequent revascularizations than anatomical testing".
Once again, this conclusion does not represent novel information. There are two previous meta-analyses that demonstrated that CCTA strategy is associated with higher rates of ICA and revascularization referrals (Bittencourt et al. Circ Cardiovasc Imaging. 2016 Apr;9(4)) and (Nielsen et al. Eur Heart J Cardiovasc Imaging 2014;15:961–971). This was also demonstrated in the large cohort study by Jorgensen et al. (J Am Coll Cardiol 2017;69:1761–70).

Reply: Regarding the meta-analysis of Bittencourt et al. (Circ Cardiovasc Imaging. 2016): The authors included 4 trials (PROMISE, SCOT-HEART, CAPP, Min et al. J Cardiovasc Comput Tomogr. 2012) comparing CCTA with "usual care". Again in this meta-analysis the authors simplified the "control arm" (labeled as "usual care") to be able to synthesize the trials through a pairwise meta-analysis. However, the "control arm" for PROMISE was actually SPECT-MPI, or stress echocardiography, or exercise-ECG, with the vast majority having received SPECT-MPI. In addition, in CAPP trial and Min et al. the "control arm" was exercise-ECG and SPECT-MPI respectively and not "usual care", as has been used by the authors. Finally, only 3 trials contributed to the meta-analyses of the outcomes of myocardial infarction and death, in contrast to our network meta-analysis in which 6 trials of CCTA contributed with information to the network for both outcomes.

Regarding the meta-analysis of Nielsen et al. (Eur Heart J Cardiovasc Imaging 2014): The authors deemed eligible studies of different design (studies of diagnostic accuracy, prospective/retrospective studies on clinical outcomes, and only 1 diagnostic randomized trials). Only the single diagnostic randomized trial has been included in our network met-analysis. Moreover, it is not clear how the authors synthesized this kind of information of completely different

design. They do not provide any details on how the addressed inherent problems in such meta-analyses.

In all the above-mentioned conventional meta-analyses, the investigators simplified the "control-arm" since they were not able to consider each individual test separately. We overcame this limitation by applying advanced statistical methods through network meta-analysis which allowed us to derive estimates for each individual diagnostic test separately and after grouping of functional tests. In addition, as we mention above, we were able to get estimates indirectly for comparisons that had never been tested head-to-head before.

We would like also to highlight the evaluation of the outcome of "overall downstream testing" (refers to the additional diagnostic investigations after the initial diagnostic test/strategy, which is typically occurred following a test failure or diagnostic uncertainty in relation to the index test result) in our network meta-analysis. This outcome has not been assessed in any of the above-mentioned meta-analyses. We were able to evaluate this outcome because of the contribution of principal investigators of 11 trials (listed in "Acknowledgements" section) with previously unpublished aggregated data (available in Appendix).

Comment: It is important to recognize, however, that the present study does provide interesting novel information. As previously mentioned, the present network meta-analysis included a broader range of RCTs investigating the most frequently used non-invasive diagnostic tests in contemporary cardiology. Therefore, they were able to provide a wider picture about the use of non-invasive testing in both acute and chronic CAD assessment, including stress Echo and, particularly, CMR (rarely contemplated in previous meta-analyses).

Reply: We thank the reviewer for this comment. At this point, we would also like to acknowledge the contribution of the 11 principal investigators that contributed with unpublished data to this comprehensive analysis. Without their contribution, we would not have been able to assess patient-oriented endpoints and overall downstream testing, since these outcomes were not systematically reported in the published documents of the trials.

Comment: 5- Regarding the ACS analyses, the authors do not report on ED cost and length of stay. I believe that these constitute relevant outcome parameters, particularly in this clinical setting. Therefore, I would suggest the authors report it for the different diagnostic strategies used in the ER.

Reply: As we mention in the previously published protocol of our network meta-analysis (PROSPERO CRD42016049442), our initial intention was to assess also additional outcomes, specifically time to diagnosis (applicable to patients suspected of ACS - time from presentation in the emergency department until the first test that led to the diagnosis), cumulative radiation exposure, length of hospitalisation during the index care of episode, and rehospitalisations for cardiac causes. However, this information was widely missing from the published reports of the trials, and even after receiving additional unpublished

data from 11 trials, we did not have adequate amount of information required for network meta-analysis calculations. ED cost had been also considered in the early phases of our study design. However, because of the expected diversity across the provided measurement of the individual studies we decided to not look into it. We definitely agree with your opinion, this is a critical outcome for the evaluation of the different diagnostic strategies used in the ER.

Reviewer: 3

Comment: The present manuscript represents an enormous effort by the authors to compile and to use the most advance techniques available to summarise the evidence of these different diagnostic techniques for detecting Coronary Artery Disease.

Reply: We thank the reviewer for their positive comment.

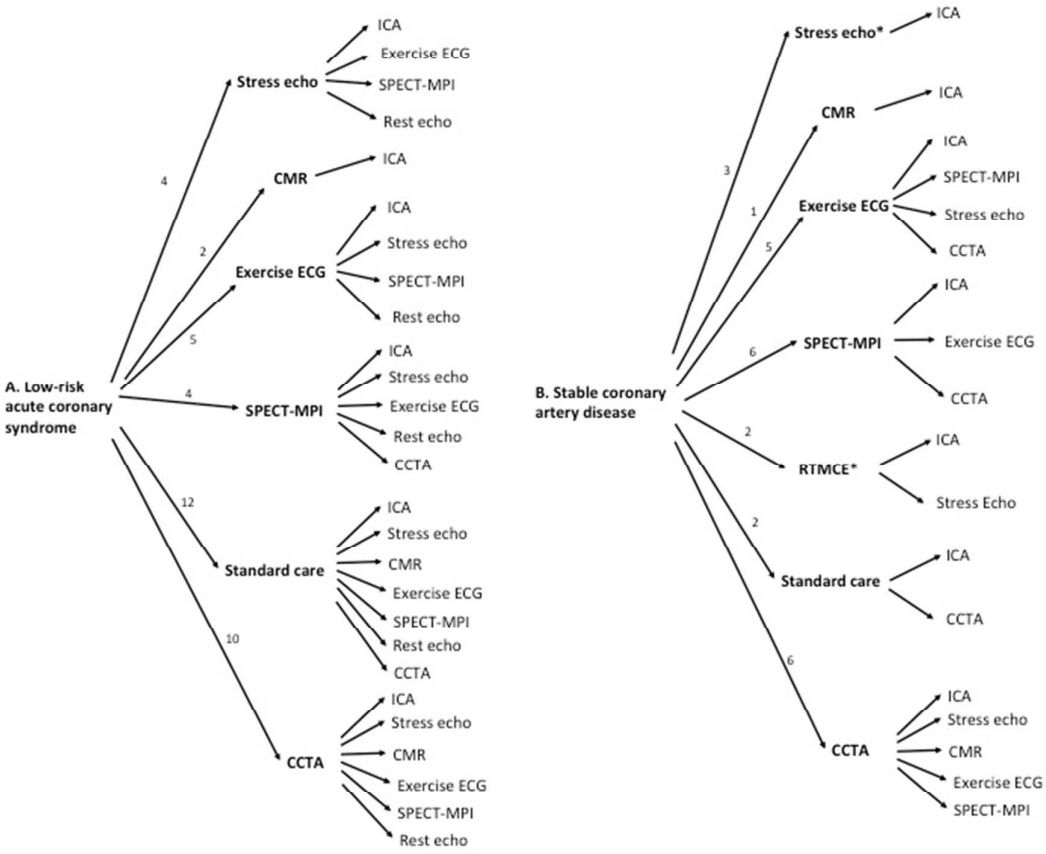
Comment: The message is as simple as can be made while maintaining a level of uncertainty required given the evidence available. It might be possible to simplify slightly (as one of the reviewers suggests) although this might make it more difficult to reply to the other reviewer challenge of how the authors have interpreted the finding of less invasive assessments and revascularizations as a positive outcome.

Reply: We have extensively revised the manuscript in response to Reviewers' 1 and 2 comments and in an effort to breakdown the messages of our work and make them widely comprehensible.

Comment: In terms of methods, the authors are experts in the N-MA field and it shows. The level or reporting and methods used are at the cutting edge in this area. As a minor note, it might be desirable (as part of the simplification process) to provide figures (as part of the full paper or as extra material) of the diagnostic pathways tested. This might help in the Introduction and certainly in the Discussion.

Reply: Thank you for your positive comment on our work. We have summarized the different diagnostic pathways tested in each diagnostic randomized controlled trial in the following figure. We have included this figure in the main manuscript.

FIGURE 2: Pathways taken following the index diagnostic intervention across the included diagnostic randomized controlled trials for low-risk acute coronary syndrome patients (Panel A) and for patients suspected of stable coronary artery disease (Panel B).
Numbers indicate the total number of trials in which each index diagnostic strategy (arm of randomization) was applied. The finally listed diagnostic strategies in each graph refer to downstream tests performed following the index diagnostic strategy.
*Information on downstream testing is missing from one trial.
Abbreviations: As in Figure 1.


A. Low-risk acute coronary syndrome
Stress echo
ICA
Exercise ECG
SPECT-MPI
Rest echo
CMR
ICA
Exercise ECG
ICA
Stress echo
SPECT-MPI
Rest echo
SPECT-MPI
ICA
Stress echo
Exercise ECG
Rest echo
CCTA
Standard care
ICA
Stress echo
CMR
Exercise ECG
SPECT-MPI
Rest echo
CCTA
CCTA
ICA
Stress echo
CMR
Exercise ECG
SPECT-MPI
Rest echo
4
2
5
4
12
10
B. Stable coronary artery disease
Stress echo*
ICA
CMR
ICA
Exercise ECG
ICA
SPECT-MPI
Stress echo
CCTA
SPECT-MPI
ICA
Exercise ECG
CCTA
RTMCE*
ICA
Stress Echo
Standard care
ICA
CCTA
CCTA
ICA
Stress echo
CMR
Exercise ECG
SPECT-MPI
3
1
5
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2
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6

Information for submitting a revision

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Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

Reply: The following Box has been added:

What is already known on this subject

- Clinicians largely rely on information of diagnostic accuracy to decide on the usefulness of a diagnostic test, which may not necessarily translate into patient benefits.
- The most conclusive evidence regarding patient outcomes can be derived from diagnostic randomized controlled trials, which represent a rigorous approach to diagnostic test evaluation.
- There is a broad range of noninvasive imaging modalities to investigate patients with suspected low-risk acute coronary syndromes or stable coronary artery disease; however the impact of these tests on downstream testing and clinical outcomes remains unknown and inconsistent.

What this study adds

- In low-risk acute coronary syndrome patients, functional testing in terms of stress echocardiography and cardiovascular magnetic resonance is associated with fewer referrals for downstream invasive coronary angiography compared with coronary computed tomographic angiography without apparent impact on the subsequent risk of myocardial infarction.
- Among patients with suspected stable coronary artery disease, functional testing in terms of stress echocardiography and single-photon emission computed tomography-myocardial perfusion imaging is associated with less requirement for additional diagnostic investigations (overall downstream testing) compared with coronary computed tomographic angiography; whereas the estimates cannot rule out a significant impact on clinical outcomes associated with individual tests.
- Future adequately powered clinical trials should evaluate more broadly defined clinical outcomes, subsequent use of hospital resources and cost-effectiveness aspects of implemented strategies, which are representative of current clinical practice.

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

Reply: Ethics committee approval was not required for this network meta-analysis, since aggregated data from published diagnostic randomized trials were summarized.

3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

Reply: Not required for the same reason mentioned above.

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

Reply: Disclosures of each author are provided in the beginning of the document as appropriate.

5. Contributorship statement+ guarantor (see http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship)

Reply: A contributorship statement is provided in the beginning of the document.

6. Transparency statement: (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/transparency-policy)

Reply: The following statement has been included in the beginning of the main manuscript: "Transparency: The corresponding author, SW, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

7. Copyright statement/licence for publication (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)

Reply: The respective statement has been included in the main manuscript.

8. Data sharing statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research)

Reply: The respective statement has been included in the main manuscript.

9. Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

Reply: The respective statement has been included in the main manuscript.

10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

Reply: Not required. The analysis was based on aggregated data of published diagnostic randomized controlled trials.

11. Please ensure the paper complies with The BMJ's style, as detailed below:

a. Title: this should include the study design eg "systematic review and meta-analysis."

Reply: Study design has been indicated in the title as appropriate.

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

Reply: This has been done.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

Reply: This has been done.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

Reply: We now provide further details and key features of each interventions (diagnostic tests)/comparators of interest (Box 1 and Box 2). Detailed information has been included as supplementary material, which enables the readers to replicate our findings.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely

used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

Reply: Dedicated statistical methods and methods of reporting have been adopted as appropriate for network meta-analyses.

f. Discussion: To minimize the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

Reply: Changes have been adopted as appropriate.